REMARKS

Claims 1-40 are pending in the subject application. Claim 5 has been amended and new claims 41-43 have been added to clarify what Applicants regard as the invention. Support for the amendment to claim 5 is found *inter alia* in the specification as filed, for example, at page 12, lines 20-21 and at page 37, lines 31-34. Support for new claims 41-43 is at page 8, lines 3-8. Claims 7, 9, 14-16, 20-22, and 26 have been amended to recite appropriate dependencies. Applicants have canceled claims 1-4, 17-19, 24, 25, and 29-40 without prejudice. Claims 27 and 28 are withdrawn as being drawn to a nonelected species. Claims 5-16, 20-23, 26, and 41-43 will be pending and under examination upon entry of this Amendment.

Formalities

The Examiner stated that pending claims 1-4, 17, 24, and 29-40 have been withdrawn as being directed to a nonelected invention and claims 27 and 28 have been withdrawn as being directed to a nonelected species. Applicants note that claims 1-4, 17, 24, and 29-40 are canceled by this Amendment.

The Examiner also stated that the specification should be amended to indicate that U.S. Serial No. 09/393,652, ("the '652 application") has been abandoned. In response, Applicants point out that the '652 application has been reinstated. Accordingly, no amendment of the specification is required.

The Examiner objected to claims 7-16, 18-23, and 25-28 because these claims depend from claims of nonelected groups. In response, Applicants have amended the claims to recite the proper dependency. The Examiner also objected to claim 25 as being of improper dependent format for failing to further limit the subject matter of the claim from which it depends. In response, Applicant notes that claim 25 has been canceled, rendering the objection moot.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 5-16, 18-23, 25, and 26 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to use the invention.

Applicants understand the Examiner's rejection to be based upon an alleged lack of examples in the specification demonstrating that administration of gp96 substantially free of complexed antigenic peptide inhibits graft rejection. The Examiner further relied upon the alleged teaching of the prior art in Attfield, U.S. Patent No. 5,891,653, that heat shock proteins uncomplexed with antigenic peptides loose their biological activity with respect to modulation of the immune response.

In response, Applicants respectfully disagree with the Examiner's position and submit that the specification enables the claimed methods of treating rejection of a grafted cell, tissue, or organ in a mammal comprising administering to the mammal a composition comprising a purified heat shock protein which is substantially free of complexed antigenic molecule. In support of their position, Applicants note that the Examples in the specification, although conducted with heat shock protein complexed with peptide, clearly indicate that the ability to inhibit graft rejection is not dependent on the tissue source of the heat shock protein, and therefore is independent of the complexed peptides, which are tissue-specific and thus vary depending on the tissue source. For example, at page 40, lines 32-37, the specification teaches that the rejection of a skin graft was effectively inhibited by heat shock protein isolated from either liver or skin tissue. Since the inhibition of graft rejection was not dependent on the tissue source of the heat shock protein, it follows that the ability to inhibit graft rejection is not dependent on the identity of the peptides complexed with the heat shock protein. Rather, as the specification teaches at page 3, lines 35-36, to page 4, line 20, the ability to inhibit graft rejection is a general property of the heat shock protein, independent of the tissue source from which it is isolated. With respect to the Examiner's reliance on Attfield, Applicants point out that the statement in Attfield at column 4, lines 29-47, indicating that heat shock protein must be complexed with peptide in order to retain its biological activity is unsubstantiated by any data or other evidence provided by Attfield. To the contrary, Applicants' specification provides evidence that the ability of heat shock protein to inhibit graft rejection is independent of the tissue source of the complexed peptide.

Accordingly, Applicants submit that the specification enables one of skill in the art to use the claimed invention in satisfaction of the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner's rejection be withdrawn.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 5-16, 18-23, and 25-26 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner objected to the reference in claim 5 to a heat shock protein "substantially free" of complexed antigenic molecule because the term "substantially free" is allegedly indefinite.

In response, Applicants respectfully submit that the reference to a heat shock protein "substantially free" of complexed antigenic molecule is clear and definite. In support of their position, Applicants submit that methods for testing whether a purified heat shock protein is substantially free of complexed antigenic molecules were commonly known and routine in the art at the time of filing. For example, it would be apparent to the skilled artisan that, to test whether a heat shock protein is substantially free of complexed antigenic molecules, one could first treat a portion of the heat shock protein preparation according to a known method for separating complexed peptides from heat shock proteins, then test either for the presence of such separated peptides or for the loss of peptide-specific antigenicity or immunogenicity. Both the prior art and the specification teach methods for separating complexed peptides from heat shock proteins, see *e.g.*, the specification at page 24, lines 30-35, and Udono and Srivastava, *J. Exp. Med.* (1993) 178:1391-96, at page 1392 ("Udono," of record as reference no. C61 of Applicants' Information Disclosure Statement mailed January 13, 2005). Routine methods of protein separation and detection, such as size exclusion chromatography, high performance liquid chromatography or absorption spectrophotometry, could be used to detect any peptides that separate from the heat shock proteins, see *e.g.*, Fig. 4 of Udono at page 1395, which shows the chromatographic detection of peptides associated with heat shock proteins. If no peptides are detected, one of skill in the art would regard the heat shock protein preparation as "substantially free" of complexed peptides. Alternatively, or in addition to the direct detection of complexed molecules, a routine biological assay for antigenicity or immunogenicity, such as a cytotoxic T cell assay using T cells sensitized to

peptides of the tissue from which the heat shock protein was isolated or a tumor immunity assay, could be used for the detection of antigenic peptides complexed to heat shock proteins. Such assays were commonly known in the art at the time of filing, see *e.g.*, Suto and Srivastava, *Science* (1995) 269:1585-88, at pages 1586-87 (of record as reference no. C57 of Applicants' Information Disclosure Statement mailed January 13, 2005); and Udono at pages 1392-1394. One of skill in the art would regard as "substantially free" of complexed antigenic molecule a heat shock protein preparation that failed to produce a biological response in such an assay for antigenicity or immunogenicity.

In view of the teaching in both the prior art and the specification of methods for treating heat shock proteins to release complexed peptides, combined with the availability of routine methods for the detection of such released peptides and for the determination of antigenic/immunogenic activity, Applicants submit that it was within the routine skill in the art to test for whether a heat shock protein preparation was substantially free of complexed antigenic molecules. Accordingly, Applicants maintain that claims 5-16, 18-23, and 25-26 satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner's rejection be withdrawn.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 5-10, 12, 14, 16, 18-22, 25, and 26 under 35 U.S.C. §102(b) as allegedly anticipated by Berberian et al., U.S. Patent No. 5,348,945, of record as reference no. A02 in Applicants' Information Disclosure Statement filed January 13, 2005.

In response to the Examiner's rejection, Applicants respectfully traverse on the ground that Berberian fails to anticipate the claimed methods because Berberian does not teach a method of treating graft rejection *in a mammal* that comprises the administration of a heat shock protein *to the mammal.*

In order to anticipate the claimed invention, a single prior art reference must teach each and every element of the claims, either expressly or inherently. *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); and *Atlas Powder Co. v. IRECO, Inc.*,190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claim 5 is directed to a method of treating rejection of a grafted cell, tissue, or organ *in a mammal* comprising administering *to a mammal* in need of such treating a composition comprising a purified heat shock protein which is substantially free of complexed antigenic molecule, wherein the heat shock protein is not cpn10 or hsp60. Claims 6-10, 12, 14, 16, 18-22, 25, and 26 depend from claim 5.

Berberian describes a number of examples in which tissue under stress *in vivo* is treated by administration of hsp70, see *e.g.*, col. 3, lines 37-68, to col. 4, line 52. However, none of the *in vivo* methods described by Berberian is a method of treating graft rejection. Instead, in the transplantation context, Berberian teaches only the treatment of tissues maintained *ex vivo* prior to transplantation, see *e.g.*, col. 3, lines 9-36. Thus, Berberian teaches the inclusion of hsp70 in organ preservation solutions used to preserve organs and tissues outside of the body. Berberian does not teach the administration of a heat shock protein to a mammal for treating graft rejection *in the mammal*, as recited by the claimed methods. Accordingly, Berberian does not anticipate claim 5 or claims 6-10, 12, 14, 16, 18-22, 25, and 26, which depend from claim 5, and Applicants respectfully request that the Examiner's rejection under 35 U.S.C. §102(b) be withdrawn.

Obviousness-Type Double Patenting

The Examiner rejected claims 5-7, 9-16, 18-23, 25 and 26 as allegedly unpatentable over claims 4, 9, 11, 22, 31, and 39 of U.S. Patent No. 6,007,821 ("the '821 patent") under the judicially created doctrine of obviousness-type double patenting. The Examiner stated that although the claims are not identical, they are not patentably distinct from each other because the patented claims, directed to a method of treating autoimmune disease using heat shock proteins that are not complexed with antigenic peptides, anticipate the presently claimed invention. In support of the rejection, the Examiner pointed to the specification of the '821 patent which describes islet cell transplantation as a form of treatment of autoimmune disease.

Applicants respectfully submit that claims 4, 9, 11, 22, 31, and 39 of the '821 patent, which are directed to a method of *treating an autoimmune disease* by administering a composition comprising heat shock proteins, do not render obvious the claimed methods of

treating rejection of a grafted cell, tissue, or organ by administering a composition comprising heat shock proteins.

The legal standard for an obviousness-type double patenting rejection requires a comparison of what is *claimed* in the earlier patent, not what was disclosed in the specification of the earlier patent. See *e.g.*, *General Foods, Inc. v. Studiengesellschaft Köhle mbH,* 972 F.2d 1272, 1280-81 (Fed. Cir. 1992). Although the specification may be used to determine the meaning of terms used in the claims, the specification may not be used as prior art. See *e.g., In re Vogel*, 422 F.2d 438 (C.C.P.A. 1970).

Applicants submit that the claims of the '821 patent directed to *treating an autoimmune disease* do not explicitly disclose or render obvious the subject claims directed to *treating rejection* of a grafted cell, tissue, or organ, for the following reasons. First, Applicants point out that treating an "autoimmune" disease would not suggest to one skilled in the art treating "graft rejection." This is because of the commonly known distinctions between the two disorders: an autoimmune disease involves an immune response against self antigen(s), *i.e.*, the autoimmune antigen, while graft rejection involves an immune response against non-self, *i.e.*, foreign antigen(s) (alloantigen(s)) (see *e.g.*, the specification at page 1, line 30, to page 2, line 9). Thus, these disorders are clearly distinguishable and treating one does not suggest treating the other. Even with respect to claim 22 of the '821 patent, which recites carrying out a transplantation procedure, such a claim merely recites performing the transplanting, rather than any effect, such as treatment, on rejection of the transplant. Merely performing a transplant does not disclose or suggest treating rejection of the transplant.

Applicants further point out that the recited claims of the '821 patent do not inherently anticipate the claimed method of treating graft rejection because performing the method of these claims would not necessarily result in treating rejection of the transplant. In order to establish inherency, "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999)(quoting *Continental Can Co. v. Monsanto Co.*, 948, F.2d 1264, 1268 (Fed. Cir. 1991)(internal quotations omitted)). In *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), the court determined that a reference that taught administering buspirone in three daily 10 mg

doses for treating anxiety failed to inherently anticipate the claimed method of administering a single dose of 20-40 mg of buspirone at bedtime for treating sleep apnea, because, *inter alia*, administering the doses of buspirone at unspecified times throughout the day in conjunction with a 10 mg dose at bedtime would not necessarily result in a therapeutically effective amount for the purpose of treating the underlying sleep apnea disorder. "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Id.* at 1063 (quoting *Continental Can Co. v. Monsanto Co.*, 948, F.2d 1264, 1269 (Fed. Cir. 1991)).

Claims 4, 9, 11, 31, and 39 of the '821 patent do not recite a transplant, and thus clearly do not inherently anticipate the instantly claimed invention since they do not inevitably result in treatment of graft rejection. Regarding claim 22, Applicants understand the Examiner's position to be that performing the method of claim 22 would necessarily result in treating graft rejection because, according to the specification, the heat shock protein immunotherapy *protects the transplanted cells* from autoimmune attack (see pages 8-9 of the April 7, 2005 Office Action). Applicants respectfully submit that practicing the method of claim 22 will not necessarily *treat rejection* of the transplant recited in claim 22. This is at least because (1) not every transplant is rejected; and (2) claim 22 does not specify *when* the heat shock proteins are administered relative to the transplantation being performed. Regarding point (2), since graft rejection can only occur after transplantation of the graft, and thus treating graft rejection can only occur after transplantation of a graft, the administered heat shock proteins would only treat any rejection of the graft that might occur if the heat shock proteins were administered near enough to the relevant time frame in which rejection was occurring. Claim 22 does not require that the heat shock proteins be administered after transplantation. Thus, for example, heat shock proteins administered well prior to rejection could not inevitably treat the rejection. Thus, there is no inherent anticipation of the instantly claimed subject matter by claim 22.

In summary, Applicants submit that claims 5-7, 9-16, 19-23, 25 and 26 are patentably distinct from claims 4, 9, 11, 22, 31, and 39 of the '821 patent and respectfully request that the Examiner's rejection under the judicially created doctrine of obviousness-type double patenting be withdrawn.

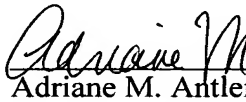
CONCLUSION

Entry of the foregoing amendment and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the remarks and amendments made herein now place the claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

It is estimated that no fee is due; however in the event that a fee is required, please charge any required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: August 5, 2005



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